

=> d his 1

(FILE 'MEDLINE, HCPLUS, BIOSIS, EMBASE, WPIDS, SCISEARCH, AGRICOLA'
ENTERED AT 10:10:35 ON 21 DEC 2004)

SET DUPORDER FILE

L28 33 DUP REM L27 (64 DUPLICATES REMOVED)

=> d que 128

L1 128 SEA LAUGHON A?/AU
 L2 21 SEA L1 AND TGF?
 L3 24 SEA L1 AND TRANSFORMING(3A) GROWTH(3A) FACTOR#
 L4 25 SEA L2 OR L3
 L5 20 SEA L4 AND SMAD?
 L7 6 SEA L5 AND ?REPRESS?
 L8 9867 SEA SMAD
 L9 284 SEA DNA(3A) BIND?(5A) (COREPRESS? OR CO(A) REPRESS?)
 L10 11 SEA L9 AND SMAD?
 L11 225 SEA SMAD?(5A) (COREPRESS? OR CO(A) REPRESS?)
 L12 187 SEA L11 AND (BIND? OR INTERACT?)
 L13 164 SEA L12 AND (TGF(A) BETA OR TRANSFORMING(3A) GROWTH(3A)
 FACTOR#(A) BETA OR ACTIVIN? OR BMP? OR BONE(3A) MORPHOGEN?)
 L14 107 SEA L13 AND REPRESS?(5A) TRANSCRI?
 L15 54 SEA L14 AND (ASSAY? OR DETECT? OR IDENTIF? OR MEASUR?)
 L17 327 SEA L8 AND BOX?
 L18 22 SEA L17 AND (COREPRESS? OR CO(A) REPRESS?)
 L19 7 SEA L18 AND CTBP?
 L20 6 SEA L18 AND C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?
 L21 36 SEA L8 AND (CTBP? OR C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?) AND
 (COREPRES? OR CO(A) REPRESS?) AND (EVI? OR TGIF? OR SIP? OR
 SCHNURRI)
 L22 193 SEA L8 AND (DROSOPHILA(3A) MAD? OR MEDEA)
 L23 112 SEA L22 AND (ASSAY? OR DETECT? OR IDENTIF? OR MEASUR?)
 L24 99 SEA L23 AND (TGF(A) BETA OR TRANSFORMING(3A) GROWTH(3A)
 FACTOR#(A) BETA OR ACTIVIN? OR BMP? OR BONE(3A) MORPHOGEN?)
 L25 2 SEA L24 AND (CTBP? OR C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?)
 L26 3 SEA L8 AND (DCTBP OR CTBP2 OR CTBP(A) 2)
 L27 97 SEA L7 OR L10 OR L15 OR L19 OR L20 OR L21 OR L25 OR L26
 L28 33 DUP REM L27 (64 DUPLICATES REMOVED)

=> d ibib abs 128 1-33

L28 ANSWER 1 OF 33	MEDLINE on STN	DUPLICATE 2
ACCESSION NUMBER:	2003314351	MEDLINE
DOCUMENT NUMBER:	PubMed ID: 12714599	
TITLE:	Interaction between Smad-interacting protein-1 and the corepressor C-terminal binding protein is dispensable for transcriptional repression of E-cadherin.	
AUTHOR:	van Grunsven Leo A; Michiels Christine; Van de Putte Tom; Nelles Luc; Wuytens Gunther; Verschueren Kristin; Huylebroeck Danny	
CORPORATE SOURCE:	Department of Developmental Biology (VIB7), Flanders Interuniversity Institute for Biotechnology (VIB) and Laboratory of Molecular Biology (Celgen), University of Leuven, Herestraat 49, B-3000 Leuven, Belgium.	
SOURCE:	Journal of biological chemistry, (2003 Jul 11) 278 (28) 26135-45.	
PUB. COUNTRY:	Journal code: 2985121R. ISSN: 0021-9258. United States	
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)	
LANGUAGE:	English	
FILE SEGMENT:	Priority Journals	
ENTRY MONTH:	200308	
ENTRY DATE:	Entered STN: 20030708 Last Updated on STN: 20030815	

Entered Medline: 20030814

AB deltaEF1 and **SIP1** (or Zfhx1a and Zfhx1b, respectively) are the only known members of the vertebrate Zfh1 family of homeodomain/zinc finger-containing proteins. Similar to other transcription factors, both **Smad**-interacting protein-1 (**SIP1**) and deltaEF1 are capable of repressing E-cadherin transcription through binding to the E2 boxes located in its promoter. In the case of deltaEF1, this repression has been proposed to occur via interaction with the **corepressor C-terminal binding protein (CtBP)**. In this study, we show by coimmunoprecipitation that **SIP1** and **CtBP** interact in vivo and that an isolated **CtBP**-binding **SIP1** fragment depends on **CtBP** for transcriptional repression. However, and most importantly, full-length **SIP1** and deltaEF1 proteins do not depend on their interaction with **CtBP** to repress transcription from the E-cadherin promoter. Furthermore, in E-cadherin-positive kidney epithelial cells, the conditional synthesis of mutant **SIP1** that cannot bind to **CtBP** abrogates endogenous E-cadherin expression in a similar way as wild-type **SIP1**. Our results indicate that full-length **SIP1** can repress E-cadherin in a **CtBP**-independent manner.

L28 ANSWER 2 OF 33 MEDLINE on STN DUPLICATE 3
 ACCESSION NUMBER: 2003570374 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14645520
 TITLE: **Smad6 recruits transcription corepressor CtBP to repress bone morphogenetic protein-induced transcription.**
 AUTHOR: Lin Xia; Liang Yao-Yun; Sun Baohua; Liang Min; Shi Yujiang; Brunicardi F Charles; Shi Yang; Feng Xin-Hua
 CORPORATE SOURCE: Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, Room 131D, Houston, TX 77030,
 USA.. xialin@bcm.tmc.edu
 CONTRACT NUMBER: F32 GM 70690 (NIGMS)
 R01 CA 95731 (NCI)
 R01 GM 53874 (NIGMS)
 R01 GM 63773 (NIGMS)
 SOURCE: Molecular and cellular biology, (2003 Dec) 23 (24) 9081-93.
 Journal code: 8109087. ISSN: 0270-7306.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200401
 ENTRY DATE: Entered STN: 20031216
 Last Updated on STN: 20040117
 Entered Medline: 20040116

AB Smad6 and Smad7 are inhibitory Smads induced by **transforming growth factor beta-Smad** signal transduction pathways in a negative-feedback mechanism. Previously it has been thought that inhibitory Smads bind to the type I receptor and block the phosphorylation of receptor-activated Smads, thereby inhibiting the initiation of **Smad** signaling. Conversely, few studies have suggested the possible nuclear functions of inhibitory Smads. Here, we present compelling **evidence** demonstrating that Smad6 **repressed bone morphogenetic protein-induced Id1 transcription** through recruiting transcriptional **corepressor C-terminal binding protein (CtBP)**. A consensus **CtBP-binding motif, PLDLS**, was identified in the linker region of Smad6. Our findings show that mutation in the motif abolished the Smad6 **binding to CtBP** and subsequently its **repressor activity of transcription**. We conclude that the nuclear functions and physical **interaction** of Smad6 and **CtBP** provide a novel mechanism for the transcriptional regulation

by inhibitory Smads.

L28 ANSWER 3 OF 33 MEDLINE on STN DUPLICATE 4
 ACCESSION NUMBER: 2003221346 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12743039
 TITLE: Regulation of **Smad** signaling through a differential recruitment of coactivators and **corepressors** by ZEB proteins.
 AUTHOR: Postigo Antonio A; Depp Jennifer L; Taylor Jennifer J; Kroll Kristen L
 CORPORATE SOURCE: Division of Molecular Oncology, Department of Internal Medicine, Washington University School of Medicine, St Louis, MO 63110, USA.. apostigo@im.wustl.edu
 SOURCE: EMBO journal, (2003 May 15) 22 (10) 2453-62.
 Journal code: 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200307
 ENTRY DATE: Entered STN: 20030514
 Last Updated on STN: 20030715
 Entered Medline: 20030714

AB Balancing signals derived from the TGFbeta family is crucial for regulating cell proliferation and differentiation, and in establishing the embryonic axis during development. TGFbeta/BMP signaling leads to the activation and nuclear translocation of **Smad** proteins, which activate transcription of specific target genes by recruiting P/CAF and p300. The two members of the ZEB family of zinc finger factors (ZEB-1/deltaEF1 and ZEB-2/**SIP1**) regulate TGFbeta/BMP signaling in opposite ways: ZEB-1/deltaEF1 synergizes with **Smad**-mediated transcriptional activation, while ZEB-2/**SIP1** represses it. Here we report that these antagonistic effects by the ZEB proteins arise from the differential recruitment of transcriptional coactivators (p300 and P/CAF) and **corepressors** (**CtBP**) to the Smads. Thus, while ZEB-1/deltaEF1 binds to p300 and promotes the formation of a p300-**Smad** transcriptional complex, ZEB-2/**SIP1** acts as a repressor by recruiting **CtBP**. This model of regulation by ZEB proteins also functions *in vivo*, where they have opposing effects on the regulation of TGFbeta family-dependent genes during *Xenopus* development.

L28 ANSWER 4 OF 33 MEDLINE on STN DUPLICATE 5
 ACCESSION NUMBER: 2003159343 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12593671
 TITLE: Regulation of TG-interacting factor by transforming growth factor-beta.
 AUTHOR: Chen Feifei; Ogawa Kenji; Nagarajan Raman P; Zhang Meiyu; Kuang Chenzhong; Chen Yan
 CORPORATE SOURCE: Department of Medical Molecular Genetics, the Walther Oncology Center, Indiana University School of Medicine, the Walther Cancer Institute, Indianapolis, IN 46202, USA.
 CONTRACT NUMBER: R01 DK55991 (NIDDK)
 SOURCE: Biochemical journal, (2003 Apr 15) 371 (Pt 2) 257-63.
 Journal code: 2984726R. ISSN: 0264-6021.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200307
 ENTRY DATE: Entered STN: 20030406
 Last Updated on STN: 20030704
 Entered Medline: 20030703

AB TG-interacting factor (TGIF) is a transcriptional co-repressor that directly associates with **Smad** (Sma- and Mad-related protein) proteins and inhibits Smad-mediated

transcriptional activation. By using Affymetrix (Santa Clara, CA, U.S.A.) oligonucleotide microarray analysis, we found that TGIF mRNA level was elevated by **transforming-growth-factor-beta (TGF-beta)** treatment in a human T-cell line, HuT78. Subsequent reverse-transcription PCR assays indicated that TGF-beta1 and activin were able to induce a rapid and transient increase in the level of TGIF in both HuT78 and HepG2 hepatoma cells. To analyse whether or not the regulation of TGIF mRNA occurs at the transcriptional level, a 2.4 kb human TGIF promoter was isolated. A primer extension assay was performed to localize the putative transcription initiation site of the promoter. When transiently expressed in HepG2 cells, this promoter was stimulated by TGF-beta1 and activin treatment in a time-dependent manner. A series of deletion mutants of the TGIF promoter were also generated to further characterize the **TGF-beta** responsive region of the promoter. In addition, expression of TGIF was able to cause a dose-dependent inhibition of **TGF-beta** and activin signalling. Taken together, these experiments indicated that TGIF is a novel transcriptional target of **TGF-beta** and activin signalling and is likely involved in a negative feedback loop to desensitize **TGF-beta/activin** action.

L28 ANSWER 5 OF 33 MEDLINE on STN DUPLICATE 7
 ACCESSION NUMBER: 2003008596 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12485160
 TITLE: Two major Smad pathways in **TGF-beta** superfamily signalling.
 AUTHOR: Miyazawa Keiji; Shinozaki Masahiko; Hara Takane; Furuya Toshio; Miyazono Kohei
 CORPORATE SOURCE: Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Japan.
 SOURCE: Genes to cells : devoted to molecular & cellular mechanisms, (2002 Dec) 7 (12) 1191-204. Ref: 136 Journal code: 9607379. ISSN: 1356-9597.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200312
 ENTRY DATE: Entered STN: 20030108
 Last Updated on STN: 20031218
 Entered Medline: 20031217

AB Members of the **transforming growth factor-beta (TGF-beta)** superfamily bind to two different serine/threonine kinase receptors, i.e. type I and type II receptors. Upon ligand binding, type I receptors specifically activate intracellular Smad proteins. R-Smads are direct substrates of type I receptors; Smads 2 and 3 are specifically activated by activin/nodal and **TGF-beta** type I receptors, whereas Smads 1, 5 and 8 are activated by BMP type I receptors. Nearly 30 proteins have been identified as members of the **TGF-beta** superfamily in mammals, and can be classified based on whether they activate activin/**TGF-beta**-specific R-Smads (AR-Smads) or BMP-specific R-Smads (BR-Smads). R-Smads form complexes with Co-Smads and translocate into the nucleus, where they regulate the transcription of target genes. AR-Smads bind to various proteins, including transcription factors and transcriptional co-activators or co-repressors, whereas BR-Smads interact with other proteins less efficiently than AR-Smads. Id proteins are induced by BR-Smads, and play important roles in exhibiting some biological effects of BMPs. Understanding the mechanisms of **TGF-beta** superfamily

signalling is thus important for the development of new ways to treat various clinical diseases in which **TGF-beta** superfamily signalling is involved.

L28 ANSWER 6 OF 33 MEDLINE on STN DUPLICATE 9
 ACCESSION NUMBER: 2001276206 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11278756
 TITLE: Ski-interacting protein interacts with **Smad** proteins to augment transforming growth factor-beta-dependent transcription.
 AUTHOR: Leong G M; Subramaniam N; Figueroa J; Flanagan J L; Hayman M J; Eisman J A; Kouzmenko A P
 CORPORATE SOURCE: Bone & Mineral Research Program, Garvan Institute of Medical Research, Darlinghurst, New South Wales 2010, Australia.. g.leong@garvan.unsw.edu.au
 CONTRACT NUMBER: CA28146 (NCI)
 SOURCE: Journal of biological chemistry, (2001 May 25) 276 (21) 18243-8.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200107
 ENTRY DATE: Entered STN: 20010709
 Last Updated on STN: 20030105
 Entered Medline: 20010705

AB Transforming growth factor-beta (TGF-beta) signaling requires the action of **Smad** proteins in association with other **DNA-binding** factors and coactivator and **corepressor** proteins to modulate target gene transcription. **Smad2** and **Smad3** both associate with the c-Ski and Sno oncoproteins to repress transcription of **Smad** target genes via recruitment of a nuclear corepressor complex. Ski-interacting protein (SKIP), a nuclear hormone receptor coactivator, was examined as a possible modulator of transcriptional regulation of the TGF-beta-responsive promoter from the plasminogen activator inhibitor gene-1. SKIP augmented TGF-beta-dependent transactivation in contrast to Ski/Sno-dependent repression of this reporter. SKIP interacted with **Smad2** and **Smad3** proteins in vivo in yeast and in mammalian cells through a region of SKIP between amino acids 201-333. In vitro, deletion of the Mad homology domain 2 (MH2) domain of **Smad3** abrogated SKIP binding, like Ski/Sno, but the MH2 domain of **Smad3** alone was not sufficient for protein-protein interaction. Overexpression of SKIP partially overcame Ski/Sno-dependent repression, whereas Ski/Sno overexpression attenuated SKIP augmentation of TGF-beta-dependent transcription. Our results suggest a potential mechanism for transcriptional control of TGF-beta signaling that involves the opposing and competitive actions of SKIP and **Smad** MH2-interacting factors, such as Ski and/or Sno. Thus, SKIP appears to modulate both TGF-beta and nuclear hormone receptor signaling pathways.

L28 ANSWER 7 OF 33 MEDLINE on STN DUPLICATE 10
 ACCESSION NUMBER: 2001276203 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11262410
 TITLE: **Repression** of dpp targets by binding of brinker to mad sites.
 AUTHOR: Kirkpatrick H; Johnson K; Laughon A
 CORPORATE SOURCE: Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin 53706, USA.
 SOURCE: Journal of biological chemistry, (2001 May 25) 276 (21) 18216-22.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20030105
Entered Medline: 20010705

AB Signaling by decapentaplegic (Dpp), a Drosophila member of the **transforming growth factor (TGF)** beta superfamily of growth factors, has recently been shown to activate targets such as vestigial (vg) indirectly through negative regulation of brinker (brk). Here we show that the Brk protein functions as a **repressor** by binding to Dpp response elements. The Brk DNA binding activity was localized to an amino-terminal region containing a putative homeodomain. Brk bound to a Dpp response element of the Ultrabithorax (Ubx) midgut enhancer at a sequence that overlaps a binding site for the **Smad** protein, Mothers Against Dpp (Mad). Furthermore, Brk was able to compete with Mad for occupancy of this binding site. This recognition of overlapping binding sites provides a potential explanation for why the G/C-rich Mad binding site consensus differs the **Smad3/Smad4** binding site consensus. We also found that the Dpp response element from Ubx was more sensitive than the vg quadrant enhancer to **repression** by Brk. This difference correlates with short-range activation of Ubx by Dpp in the visceral mesoderm, whereas vg exhibits a long-range response to Dpp in the wing imaginal disc, indicating that Brk binding sites may play a critical role in limiting thresholds for activation by Dpp. Finally, we provide evidence that Brk is capable of functioning as an active **repressor**. Thus, whereas Brk and Mad compete for regulation of Ubx and vg, Brk may regulate other Dpp targets without direct involvement of Mad.

L28 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2001340867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11313276
TITLE: The **corepressor CtBP** interacts with **Evi-1** to repress transforming growth factor beta signaling.
AUTHOR: Izutsu K; Kurokawa M; Imai Y; Maki K; Mitani K; Hirai H
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Japan.
SOURCE: Blood, (2001 May 1) 97 (9) 2815-22.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB **Evi-1** is a zinc finger nuclear protein whose inappropriate expression leads to leukemic transformation of hematopoietic cells in mice and humans. This was previously shown to block the antiproliferative effect of transforming growth factor beta (TGF-beta). **Evi-1** represses TGF-beta signaling by direct interaction with Smad3 through its first zinc finger motif. Here, it is demonstrated that **Evi-1** represses Smad-induced transcription by recruiting **C-terminal binding protein (CtBP)** as a **corepressor**. **Evi-1** associates with **CtBP1** through one of the consensus binding motifs, and this association is required for efficient inhibition of TGF-beta signaling. A specific inhibitor for histone deacetylase (HDAC) alleviates **Evi-1**-mediated repression of TGF-beta signaling, suggesting that HDAC is involved in the transcriptional repression by **Evi-1**. This identifies a novel function of **Evi-1** as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms for **Evi-1**-induced

leukemogenesis.

L28 ANSWER 9 OF 33 MEDLINE on STN DUPLICATE 12
 ACCESSION NUMBER: 2001316649 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11389444
 TITLE: **TGF-beta** induces assembly of a Smad2-Smurf2 ubiquitin ligase complex that targets SnoN for degradation.
 AUTHOR: Bonni S; Wang H R; Causing C G; Kavsak P; Stroschein S L; Luo K; Wrana J L
 CORPORATE SOURCE: Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada.
 SOURCE: Nature cell biology, (2001 Jun) 3 (6) 587-95.
 Journal code: 100890575. ISSN: 1465-7392.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200109
 ENTRY DATE: Entered STN: 20010924
 Last Updated on STN: 20030304
 Entered Medline: 20010920

AB The receptor-regulated Smad proteins are essential intracellular mediators of signal transduction by the **transforming growth factor-beta (TGF-beta)** superfamily of growth factors and are also important as regulators of gene transcription. Here we describe a new role for **TGF-beta**-regulated Smad2 and Smad3 as components of a ubiquitin ligase complex. We show that in the presence of **TGF-beta** signalling, Smad2 interacts through its proline-rich PPXY motif with the tryptophan-rich WW domains of Smurf2, a recently identified E3 ubiquitin ligases. **TGF-beta** also induces the association of Smurf2 with the transcriptional co-repressor SnoN and we show that Smad2 can function to mediate this interaction. This allows Smurf2 HECT domain to target SnoN for ubiquitin-mediated degradation by the proteasome. Thus, stimulation by **TGF-beta** can induce the assembly of a Smad2-Smurf2 ubiquitin ligase complex that functions to target substrates for degradation.

L28 ANSWER 10 OF 33 MEDLINE on STN DUPLICATE 13
 ACCESSION NUMBER: 2001540678 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11587364
 TITLE: Oncogenic mechanisms of **Evi-1** protein.
 AUTHOR: Hirai H; Izutsu K; Kurokawa M; Mitani K
 CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Hongo, Japan.. hhirai-tky@umin.ac.jp
 SOURCE: Cancer chemotherapy and pharmacology, (2001 Aug) 48 Suppl 1 S35-40. Ref: 29
 Journal code: 7806519. ISSN: 0344-5704.
 PUB. COUNTRY: Germany: Germany, Federal Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200110
 ENTRY DATE: Entered STN: 20011008
 Last Updated on STN: 20011015
 Entered Medline: 20011011
 AB Although **Evi-1** is thought to promote growth or block differentiation in some cell types, its biological functions have not been elucidated. To explore the mechanisms underlying **Evi-1**-induced oncogenesis, we investigated whether **Evi-1** affects the signaling

of transforming growth factor beta (TGF-beta), which inhibits proliferation of a wide range of cell types and is one of the most studied growth regulatory factors. We demonstrated that **Evi-1** represses TGF-beta signaling and antagonizes its growth-inhibitory effects. Two separate regions of **Evi-1** are responsible for this repression, one of which is the first zinc-finger domain. Through this domain, **Evi-1** physically interacts with Smad3, an intracellular mediator of TGF-beta signaling, thereby suppressing the transcriptional activity of Smad3. These results define a novel function of **Evi-1** as a repressor of signaling components of TGF-beta. We also demonstrated that **Evi-1** represses Smad-induced transcriptional activation by recruiting **CtBP** as a **corepressor**. **Evi-1** associates with **CtBP1** through one of the **CtBP**-binding consensus motifs within the region from amino acid 544 to 607, and this association is required for the efficient inhibition of TGF-beta signaling. A specific histone deacetylase (HDAC) inhibitor, trichostatin A (TSA), alleviates **Evi-1**-mediated repression of TGF-beta signaling, suggesting that HDAC is involved in transcriptional repression by **Evi-1**. This identifies a novel function of **Evi-1** as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms involved in **Evi-1**-induced leukemogenesis. These results indicate that specific HDAC inhibitors may be useful in the treatment of **Evi-1**-induced neoplastic tumors, including myeloid leukemias.

L28 ANSWER 11 OF 33 MEDLINE on STN DUPLICATE 14
 ACCESSION NUMBER: 2001106053 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10995736
 TITLE: The interaction of the carboxyl terminus-binding protein with the Smad corepressor TGIF is disrupted by a holoprosencephaly mutation in TGIF.
 AUTHOR: Melhuish T A; Wotton D
 CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics and Center for Cell Signaling, University of Virginia, Charlottesville, Virginia 22908, USA.
 SOURCE: Journal of biological chemistry, (2000 Dec 15) 275 (50) 39762-6.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200102
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010208

AB The homeodomain protein **TGIF** **represses transcription** in part by recruiting histone deacetylases. **TGIF** binds directly to DNA to **repress transcription** or **interacts** with **TGF-beta**-activated Smads, thereby repressing genes normally activated by **TGF-beta**. Loss of function mutations in **TGIF** result in holoprosencephaly (HPE) in humans. One HPE mutation in **TGIF** results in a single amino acid substitution in a conserved PLDLS motif within the amino-terminal repression domain. We demonstrate that **TGIF** **interacts** with the **corepressor** carboxyl terminus-binding protein (**CtBP**) via this motif. **CtBP**, which was first identified by its ability to bind the adenovirus E1A protein, **interacts** both with gene-specific **transcriptional repressors** and with a subset of polycomb proteins. Efficient repression of **TGF-beta**-activated gene responses by **TGIF** is dependent on **interaction** with **CtBP**, and we show that **TGIF** is able to recruit **CtBP** to a **TGF-beta**-activated Smad

complex. Disruption of the PLDLS motif in **TGIF** abolishes the interaction of **CtBP** with **TGIF** and compromises the ability of **TGIF** to repress transcription.

Thus, at least one HPE mutation in **TGIF** appears to prevent **CtBP**-dependent transcriptional repression by **TGIF**, suggesting an important developmental role for the recruitment of **CtBP** by **TGIF**.

L28 ANSWER 12 OF 33 MEDLINE on STN DUPLICATE 15
 ACCESSION NUMBER: 2000283927 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10811875
 TITLE: Ski acts as a **co-repressor** with **Smad2** and **Smad3** to regulate the response to type **beta transforming growth factor**.
 AUTHOR: Xu W; Angelis K; Danielpour D; Haddad M M; Bischof O; Campisi J; Stavnezer E; Medrano E E
 CORPORATE SOURCE: Huffington Center on Aging and Departments of Molecular and Cellular Biology and Dermatology, Baylor College of Medicine and Veterans Affairs Medical Center, Houston, TX 77030, USA.
 CONTRACT NUMBER: AG-09990 (NIA)
 AG-3663 (NIA)
 CA-43600 (NCI)
 +
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2000 May 23) 97 (11) 5924-9.
 Journal code: 7505876. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200006
 ENTRY DATE: Entered STN: 20000714
 Last Updated on STN: 20000714
 Entered Medline: 20000630
 AB The c-ski protooncogene encodes a transcription factor that binds DNA only in association with other proteins. To identify co-binding proteins, we performed a yeast two-hybrid screen. The results of the screen and subsequent co-immunoprecipitation studies identified **Smad2** and **Smad3**, two transcriptional activators that mediate the type **beta transforming growth factor (TGF-beta)** response, as **Ski**-interacting proteins. In **Ski**-transformed cells, all of the **Ski** protein was found in **Smad3**-containing complexes that accumulated in the nucleus in the absence of added **TGF-beta**. DNA binding assays showed that **Ski**, **Smad2**, **Smad3**, and **Smad4** form a complex with the **Smad/Ski** binding element GTCTAGAC (SBE). **Ski** repressed **TGF-beta**-induced expression of 3TP-Lux, the natural plasminogen activator inhibitor 1 promoter and of reporter genes driven by the SBE and the related CAGA element. In addition, **Ski** repressed a **TGF-beta**-inducible promoter containing AP-1 (TRE) elements activated by a combination of Smads, Fos, and/or Jun proteins. **Ski** also repressed synergistic activation of promoters by combinations of **Smad** proteins but failed to repress in the absence of **Smad4**. Thus, **Ski** acts in opposition to **TGF-beta**-induced transcriptional activation by functioning as a **Smad**-dependent **co-repressor**. The biological relevance of this transcriptional repression was established by showing that overexpression of **Ski** abolished **TGF-beta**-mediated growth inhibition in a prostate-derived epithelial cell line.

L28 ANSWER 13 OF 33 MEDLINE on STN DUPLICATE 16
 ACCESSION NUMBER: 2000489964 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11041237
 TITLE: **TGF-beta/SMAD** signaling and its

AUTHOR: Miyazono K
 CORPORATE SOURCE: Department of Biochemistry, The Center Institute of the Japanese Foundation for Cancer Research, Tokyo, Japan..
 miyazono-ind@umin.ac.jp
 SOURCE: Biological & pharmaceutical bulletin, (2000 Oct) 23 (10) 1125-30. Ref: 73
 Journal code: 9311984. ISSN: 0918-6158.
 PUB. COUNTRY: Japan
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200102
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010222

AB Cytokines of the **transforming growth factor-beta (TGF-beta)** superfamily are multifunctional peptides that regulate growth and differentiation of various types of cells. Members of the **TGF-beta** superfamily bind to type II and type I serine/threonine kinase receptors, which mediate intracellular signals through SMAD proteins. Of 3 subtypes of SMADs, receptor-regulated SMADs are phosphorylated by the serine/threonine kinase receptors, form complexes with common-mediator SMAD, and move into the nucleus, where they act as components of transcription factor complexes. Abnormalities of the **TGF-beta** receptors and SMADs have been detected in various tumors, including colorectal cancers and pancreatic cancers. Inhibitory SMADs and transcriptional co-repressors, including c-Ski and SnoN, repress the **TGF-beta**/SMAD signaling. Perturbation of the **TGF-beta**/SMAD signaling pathway may result in progression of tumors through resistance of the cells to the growth inhibition induced by **TGF-beta**.

L28 ANSWER 14 OF 33 MEDLINE on STN DUPLICATE 17
 ACCESSION NUMBER: 2000179494 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10712925
 TITLE: **Smads** as transcriptional co-modulators.
 AUTHOR: Attisano L; Wrana J L
 CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Toronto, Toronto, M5S 1A8, Canada..
 liliana.attisano@utoronto.ca
 SOURCE: Current opinion in cell biology, (2000 Apr) 12 (2) 235-43.
 Ref: 63
 Journal code: 8913428. ISSN: 0955-0674.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200005
 ENTRY DATE: Entered STN: 20000525
 Last Updated on STN: 20000525
 Entered Medline: 20000512
 AB The **Smad** signalling pathway is critical for transmitting transforming growth factor-beta (TGF-beta) superfamily signals from the cell surface to the nucleus. In the nucleus, **Smads** regulate transcriptional responses by recruiting co-activators and co-repressors to a wide array of DNA-binding partners. Thus, **Smads** function as transcriptional co-modulators to regulate TGFbeta-dependent gene expression.

L28 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 18
 ACCESSION NUMBER: 2000044797 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10575014
 TITLE: c-Ski acts as a transcriptional co-repressor in transforming growth factor-beta signaling through interaction with smads.
 AUTHOR: Akiyoshi S; Inoue H; Hanai J; Kusanagi K; Nemoto N; Miyazono K; Kawabata M
 CORPORATE SOURCE: Department of Biochemistry, The Cancer Institute of Japanese Foundation for Cancer Research, Research for the Future Program, Japan Society for Promotion of Science, 1-37-1, Kami-ikebukuro, Toshima-ku, Tokyo 170-8455, Japan.
 SOURCE: Journal of biological chemistry, (1999 Dec 3) 274 (49) 35269-77.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200002
 ENTRY DATE: Entered STN: 20000209
 Last Updated on STN: 20000209
 Entered Medline: 20000203
 AB Smads are intracellular signaling mediators of the transforming growth factor-beta (TGF-beta) superfamily that regulates a wide variety of biological processes. Among them, Smads 2 and 3 are activated specifically by TGF-beta. We identified c-Ski as a Smad2 interacting protein. c-Ski is the cellular homologue of the v-ski oncogene product and has been shown to repress transcription by recruiting histone deacetylase (HDAC). Smad2/3 interacts with c-Ski through its C-terminal MH2 domain in a TGF-beta-dependent manner. c-Ski contains two distinct Smad-binding sites with different binding properties. c-Ski strongly inhibits transactivation of various reporter genes by TGF-beta. c-Ski is incorporated in the Smad DNA binding complex, interferes with the interaction of Smad3 with a transcriptional co-activator, p300, and in turn recruits HDAC. c-Ski is thus a transcriptional co-repressor that links Smads to HDAC in TGF-beta signaling.

L28 ANSWER 16 OF 33 MEDLINE on STN DUPLICATE 19
 ACCESSION NUMBER: 1999213492 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10199400
 TITLE: A Smad transcriptional corepressor.
 AUTHOR: Wotton D; Lo R S; Lee S; Massague J
 CORPORATE SOURCE: Cell Biology Program, Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
 CONTRACT NUMBER: CA34610 (NCI)
 GM07739 (NIGMS)
 SOURCE: Cell, (1999 Apr 2) 97 (1) 29-39.
 Journal code: 0413066. ISSN: 0092-8674.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199904
 ENTRY DATE: Entered STN: 19990511
 Last Updated on STN: 19990511
 Entered Medline: 19990427
 AB Following TGFbeta receptor-mediated phosphorylation and association with Smad4, Smad2 moves into the nucleus, binds to target promoters in association with DNA-binding cofactors, and recruits

coactivators such as p300/CBP to activate transcription. We identified the homeodomain protein TGIF as a Smad2-binding protein and a repressor of transcription. A TGFbeta-activated Smad complex can recruit TGIF and histone deacetylases (HDACs) to a Smad target promoter, repressing transcription. Thus, upon entering the nucleus, a Smad2-Smad4 complex may interact with coactivators, forming a transcriptional activation complex, or with TGIF and HDACs, forming a transcriptional repressor complex. Formation of one of these two mutually exclusive complexes is determined by the relative levels of Smad corepressors and coactivators within the cell.

L28 ANSWER 17 OF 33 MEDLINE on STN
 ACCESSION NUMBER: 2001202759 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11226163
 TITLE: Epidermal growth factor signaling via Ras controls the Smad transcriptional co-repressor TGIF.
 AUTHOR: Lo R S; Wotton D; Massague J
 CORPORATE SOURCE: Cell Biology Program, Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.
 SOURCE: EMBO journal, (2001 Jan 15) 20 (1-2) 128-36.
 Journal code: 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200104
 ENTRY DATE: Entered STN: 20010417
 Last Updated on STN: 20010417
 Entered Medline: 20010412
 AB Smad transcription factors mediate the actions of transforming growth factor-beta (TGF-beta) cytokines during development and tissue homeostasis. TGF-beta receptor-activated Smad2 regulates gene expression by associating with transcriptional co-activators or co-repressors. The Smad co-repressor TGIF competes with the co-activator p300 for Smad2 association, such that TGIF abundance helps determine the outcome of a TGF-beta response. Small alterations in the physiological levels of TGIF can have profound effects on human development, as shown by the devastating brain and craniofacial developmental defects in heterozygotes carrying a hypomorphic TGIF mutant allele. Here we show that TGIF levels modulate sensitivity to TGF-beta-mediated growth inhibition, that TGIF is a short-lived protein and that epidermal growth factor (EGF) signaling via the Ras-Mek pathway causes the phosphorylation of TGIF at two Erk MAP kinase sites, leading to TGIF stabilization and favoring the formation of Smad2-TGIF co-repressor complexes in response to TGF-beta. These results identify the first mechanism for regulating TGIF levels and suggest a potential link for Smad and Ras pathway convergence at the transcriptional level.

L28 ANSWER 18 OF 33 MEDLINE on STN
 ACCESSION NUMBER: 2002004558 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11752591
 TITLE: Crossing Smads.
 AUTHOR: Wrana J L
 CORPORATE SOURCE: Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, and Department of Medical Genetics and Microbiology, University of Toronto, Canada.. wrana@mshri.on.ca
 SOURCE: Science's STKE [electronic resource] : signal transduction knowledge environment, (2000 Mar 14) 2000 (23) RE1. Ref:

69
 Journal code: 100964423. ISSN: 1525-8882.

PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200201

ENTRY DATE: Entered STN: 20020102

Last Updated on STN: 20020125

Entered Medline: 20020122

AB The transforming growth factor-beta (TGF-beta) superfamily of secreted polypeptide growth factors exerts extensive control over all aspects of development and homeostasis, and components of this pathway are often mutated in cancers and in several hereditary disorders. Apart from TGF-beta, the superfamily also includes the activins and the bone morphogenetic proteins. These factors signal through heteromeric complexes of type II and type I serine-threonine kinase receptors, which activate the downstream Smad signal transduction pathway. Three classes of Smads have been defined: the receptor-regulated Smads (R-Smads), the common-mediator Smads (co-Smads), and the antagonistic or inhibitory Smads (I-Smads). Receptor complexes activate the Smad pathway by interacting and phosphorylating specific R-Smads. Phosphorylation of the R-Smads causes dissociation from the receptor and induces assembly into complexes with Smad4, a co-Smad. This heteromeric complex then translocates into the nucleus, where the Smads function as transcriptional co-modulators by recruiting coactivators or corepressors to Smad DNA binding partners. Thus, Smads transmit signals directly from the receptor kinase into the nucleus. Crosstalk between Smads and other signaling pathways occurs both in the cytosol and in the nucleus. In the cytosol, Smad translocation might be inhibited by mitogen-activated protein kinase-dependent phosphorylation, whereas in the nucleus Smads interact with a number of transcription factors that themselves are primary targets of other signaling pathways. Furthermore, Smad-dependent regulation of these targets often requires input from the primary signaling pathway. In these examples, Smad signaling may represent a secondary signal that modifies the output of the primary pathway. Consequently, the transcriptional response to TGF-beta family ligands may be dependent on what other signals are being received by the cell. Crosstalk may thus provide one explanation for the long-standing observation that the biological response to TGF-beta is often dependent on the extracellular environment of the cell.

L28 ANSWER 19 OF 33 HCPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:524664 HCPLUS

DOCUMENT NUMBER: 141:118208

TITLE: Repression of endogenous Smad7 by Ski

AUTHOR(S): Denissova, Natalia G.; Liu, Fang

CORPORATE SOURCE: Ernest Mario School of Pharmacy, Center for Advanced Biotechnology and Medicine and the Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Rutgers, The State Univ. New Jersey, Piscataway, NJ, 08854, USA

SOURCE: Journal of Biological Chemistry (2004), 279(27), 28143-28148

PUBLISHER: CODEN: JBCHA3; ISSN: 0021-9258

American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Ski protein has been proposed to serve as a corepressor for Smad4 to maintain a transforming growth

factor- β (TGF- β

-)-responsive promoter at a repressed, basal level. However, there have been no reports so far that it indeed acts on a natural promoter. The human Smad7 promoter has been cloned previously, and shown that it contains the 8-base pair palindromic Smad-binding element (SBE) necessary for TGF- β induction. In this report, the authors have characterized the neg. regulation of Smad7 promoter basal activity by Ski. It was shown that Ski inhibits the Smad7 promoter basal activity in a SBE-dependent manner. Mutation of the SBE abrogates the inhibitory effect of Ski on the Smad7 promoter. Moreover, mutation of the SBE increases the Smad7 promoter basal activity. Using the chromatin immunopptn. assay, it was further shown that Ski together with Smad4 binds to the endogenous Smad7 promoter. Finally, we show that RNAi knockdown of Ski increases Smad7 reporter gene activity in transient transfection assays as well as elevating the endogenous level of Smad7 mRNA. Taken together, our results provide the first evidence that Ski is indeed a corepressor for Smad4, which can inhibit a natural TGF- β responsive gene at the basal state.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2002:736875 HCAPLUS

DOCUMENT NUMBER: 137:242137

TITLE: Compositions and methods for negative regulation of TGF- β pathways

INVENTOR(S): Laughon, Allen S.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 15 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002137662	A1	20020926	US 2001-810385	20010316
WO 2002076466	A1	20021003	WO 2002-US8133	20020315
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-810385 A 20010316

AB Methods for screening for compds. that are neg. regulators of TGF- β -regulated gene expression in mammalian cells are provided, including compns. identified therefrom.

L28 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 2001:660563 HCAPLUS

DOCUMENT NUMBER: 135:317260

TITLE: TGIF2 interacts with histone deacetylase 1 and represses transcription

AUTHOR(S): Melhuish, Tiffany A.; Gallo, Christopher M.; Wotton, David

CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, 22908, USA

SOURCE: Journal of Biological Chemistry (2001), 276(34), 32109-32114

PUBLISHER: CODEN: JBCHA3; ISSN: 0021-9258
 American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB TG-interacting factor (**TGIF**) is a transcriptional repressor, which represses transcription by binding directly to DNA or interacts with transforming growth factor β (TGF β)-activated Smads, thereby repressing TGF β -responsive gene expression. Mutation of **TGIF** in humans causes holoprosencephaly, a severe genetic disorder affecting craniofacial development. Searching human expressed sequence tag data bases revealed the presence of clones encoding a **TGIF**-related protein (**TGIF2**), which contains two regions of high sequence identity with **TGIF**. Here we show that, like **TGIF**, **TGIF2** recruits histone deacetylase, but in contrast to **TGIF**, is unable to interact with the corepressor CtBP. **TGIF2** and **TGIF** have very similar DNA-binding homeodomains, and **TGIF2** represses transcription when bound to DNA via a **TGIF** binding site. **TGIF2** interacts with TGF β -activated Smads and represses TGF β -responsive transcription. **TGIF2** appears to be a context-independent transcriptional repressor, which can perform similar functions to **TGIF** and may play a role in processes, which, when disrupted by mutations in **TGIF**, cause holoprosencephaly.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:964807 HCAPLUS
 DOCUMENT NUMBER: 141:406110
 TITLE: Systems and methods for screening for modulators of neural differentiation
 INVENTOR(S): Jessel, Thomas; Wichterle, Hynek; Wilson, Sara I.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 55 pp., Cont.-in-part of U.S. Ser. No. 196,882.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224887	A1	20041111	US 2004-789308	20040226
US 2004014210	A1	20040122	US 2002-196882	20020716
PRIORITY APPLN. INFO.: US 2002-196882 A2 20020716				

AB The invention provides in vitro systems for use in identifying modulators of neural differentiation. Also provided are modulators identified by these systems. The invention further provides methods for identifying a modulator of neural differentiation, a modulator of a Wnt signaling pathway, a modulator of Wnt-dependent neural differentiation, a modulator of a BMP signaling pathway, a modulator of BMP-dependent neural differentiation, a modulator of a Hh signaling pathway, and a modulator of Hh-dependent neural differentiation. Also provided are modulators identified by these methods.

L28 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:484254 HCAPLUS
 DOCUMENT NUMBER: 141:21226
 TITLE: Molecular mechanisms of leukemogenesis by AML1/EVI-1
 AUTHOR(S): Mitani, Kinuko
 CORPORATE SOURCE: Department of Hematology, Dokkyo University School of Medicine, Tochigi, 321-0293, Japan
 SOURCE: Oncogene (2004), 23(24), 4263-4269

CODEN: ONCNES; ISSN: 0950-9232
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. The AML1/EVI-1 chimeric gene is generated by the t(3;21) (q26;q22) translocation and plays a pivotal role in progression of hematopoietic stem cell malignancies such as chronic myelocytic leukemia and myelodysplastic syndrome. In AML1/EVI-1, an N-terminal half of AML1 including a runt homol. domain is fused to the entire zinc-finger EVI-1 protein. AML1 is essential for hematopoietic cell development in fetal liver and its lineage-specific differentiation in adult. In contrast, EVI-1 is barely expressed in normal hematopoietic cells, but it is overexpressed in chronic myelocytic leukemia in blastic crisis and myelodysplastic syndrome-derived leukemia. There are at least four mechanisms identified in AML1/EVI-1 fusion protein that possibly lead into malignant transformation of hematopoietic stem cells. Firstly, AML1/EVI-1 exerts dominant-neg. effects over AML1-induced transcriptional activation. Although target genes repressed by AML1/EVI-1 are still not known, binding competition to a specific DNA sequence and histone deacetylase recruitment through a co-repressor CtBP in EVI-1 part are conceivable underlying mechanisms for the dominant-neg. effects. Secondly, AML1/EVI-1 interferes with TGF β signaling and antagonizes the growth-inhibitory effects of TGF β . The first zinc-finger domain of EVI-1 assocs. with Smad3, a TGF β signal transducer, and represses its transcriptional activity by recruiting histone deacetylase through CtBP that interacts with EVI-1. Thirdly, AML1/EVI-1 blocks JNK activity and prevents stress-induced apoptosis. AML1/EVI-1 assocs. with JNK through the first zinc-finger domain of EVI-1 and disturbs the association between JNK and its substrates. Lastly, AML1/EVI-1 enhances AP-1 activity by activating the c-Fos promoter depending on the second zinc-finger domain of EVI-1, and promotes cell proliferation. All these functions cooperatively contribute to the malignant transformation of the hematopoietic stem cells by AML1/EVI-1.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:235283 HCAPLUS
 DOCUMENT NUMBER: 140:386414
 TITLE: Interaction with Smad4 is indispensable for suppression of BMP signaling by c-Ski
 AUTHOR(S): Takeda, Masafumi; Mizuide, Masafumi; Oka, Masako; Watabe, Tetsuro; Inoue, Hirofumi; Suzuki, Hiroyuki; Fujita, Toshiro; Imamura, Takeshi; Miyazono, Kohei; Miyazawa, Keiji
 CORPORATE SOURCE: Department of Molecular Pathology and Department of Endocrinology, Graduate School of Medicine, University of Tokyo, Tokyo, 113-0033, Japan
 SOURCE: Molecular Biology of the Cell (2004), 15(3), 963-972
 CODEN: MBCEEV; ISSN: 1059-1524
 PUBLISHER: American Society for Cell Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB C-Ski is a transcriptional corepressor that interacts strongly with Smad2, Smad3, and Smad4 but only weakly with Smad1 and Smad5. Through binding to Smad proteins, c-Ski suppresses signaling of transforming growth factor- β (TGF- β) as well as bone morphogenetic proteins (BMPs). In the present study, we found that a mutant of c-Ski, termed c-Ski (ARPG) inhibited TGF- β /activin signaling but not BMP signaling. Selectivity was confirmed in luciferase reporter assays and by determination of cellular responses in mammalian

cells (**BMP**-induced osteoblastic differentiation of C2C12 cells and **TGF- β** -induced epithelial-to-mesenchymal trans-differentiation of NMuMG cells) and *Xenopus* embryos. The ARPG mutant recruited histone deacetylases 1 (HDAC1) to the Smad3-Smad4 complex but not to the Smad1/5-Smad4 complex. C-Ski (ARPG) was unable to interact with Smad4, and the selective loss of suppression of **BMP** signaling by c-Ski (ARPG) was attributed to the lack of Smad4 binding. We also found that c-Ski interacted with Smad3 or Smad4 without disrupting Smad3-Smad4 heteromer formation. C-Ski (ARPG) would be useful for selectively suppressing **TGF-.beta** ./activin signaling.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:304627 HCAPLUS
 DOCUMENT NUMBER: 139:95599
 TITLE: **Smad4** as a Transcription Corepressor for Estrogen Receptor α
 AUTHOR(S): Wu, Liyu; Wu, Yalei; Gathings, Bill; Wan, Mei; Li, Xuelin; Grizzle, William; Liu, Zhiyong; Lu, Chongyuan; Mao, Zhengkuan; Cao, Xu
 CORPORATE SOURCE: School of Medicine, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA
 SOURCE: Journal of Biological Chemistry (2003), 278(17), 15192-15200
 CODEN: JBCHA3; ISSN: 0021-9258
 PUBLISHER: American Society for Biochemistry and Molecular Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Antiestrogen compds. exhibit a variety of different effects in different tissues and are widely used for the treatment of osteoporosis, breast cancer, and other diseases. Upon examining the mol. mechanisms, we found that Smad4, a common signal transducer in the **bone morphogenetic protein (BMP)/transforming growth factor- β (TGF- β)** signaling pathway, functions as a transcription corepressor for human estrogen receptor α (ER α). Endogenous ER α was co-immunopptd. with Smad4, and the interaction was induced by antiestrogen ligands such as tamoxifen, raloxifene, and droloxifene, which was confirmed in chromatin immunopptn. assays. Smad4 and ER α form a complex when ER α binds to the estrogen-responsive element within the estrogen target gene promoter. Importantly, the expression of Smad4 inhibits both antiestrogen-induced luciferase activity and estrogen downstream target gene transcription in breast cancer cells. Mapping of the interaction domains indicates that the activation function 1 (AF1) domain of ER α is essential for its interaction with Smad4, while the MHI domain and linker region of Smad4 are essential for the interaction. Our findings represent a novel mechanism that **TGF-.beta** may regulate cell fate through Smad4-mediated cross-talk with estrogen.
 REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:937303 HCAPLUS
 DOCUMENT NUMBER: 138:20443
 TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
 INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikuo
 PATENT ASSIGNEE(S): Takara Bio Inc., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.

CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A 20010314
			JP 2001-74993	A 20010315
			JP 2001-102519	A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L28 ANSWER 27 OF 33 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:223453 HCPLUS
 DOCUMENT NUMBER: 133:145823
 TITLE: Smad6 as a transcriptional corepressor
 AUTHOR(S): Bai, Shuting; Shi, Xingming; Yang, Xiangli; Cao, Xu
 CORPORATE SOURCE: Department of Pathology, University of Alabama School of Medicine, Birmingham, AL, 35294, USA
 SOURCE: Journal of Biological Chemistry (2000), 275(12), 8267-8270
 PUBLISHER: American Society for Biochemistry and Molecular Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Smad6 and Smad7, a subgroup of Smad proteins, antagonize the signals elicited by transforming growth factor-*beta*. These two Smads, induced by transforming growth factor- β or bone morphogenetic protein (BMP) stimulation, form stable assocns. with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here the authors show that Smad6 interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between Smad6 and Hoxc-8 was identified by a yeast two-hybrid approach and further demonstrated by co-immunopptn. assays in cells. Gel shift assays show that Smad6, but not Smad7, interacts with both Hoxc-8 and Hoxa-9 as a heterodimer when binding to DNA. More importantly, the Smad6-Hoxc-8 complex inhibits interaction of Smad1 with Hoxc-8- and Smad1-induced transcription activity. These data indicate that Smad6 interacts with Hox transcription factors as part of the neg. feedback circuit in the BMP signaling pathway.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 28 OF 33 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2001:301470 BIOSIS
 DOCUMENT NUMBER: PREV200100301470

TITLE: The **corepressor CtBP** is involved in
Evi-1 mediated repression of TGF-beta signaling.
 AUTHOR(S): Izutsu, Koji [Reprint author]; Kurokawa, Mineo [Reprint
 author]; Imai, Yoichi [Reprint author]; Mitani, Kinuko
 [Reprint author]; Hirai, Hisamaru [Reprint author]
 CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of
 Medicine, University of Tokyo, Tokyo, Japan
 SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 90a.
 print.
 Meeting Info.: 42nd Annual Meeting of the American Society
 of Hematology. San Francisco, California, USA. December
 01-05, 2000. American Society of Hematology.
 CODEN: BLOOAW. ISSN: 0006-4971.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Jun 2001
 Last Updated on STN: 19 Feb 2002
 AB **Evi-1** is a zinc finger nuclear protein whose inappropriate expression leads to leukemic transformation of hematopoietic cells in mice and humans. **Evi-1** is shown to be highly expressed in human myeloid leukemias and myelodysplastic syndromes by chromosomal rearrangements involving 3q26. It is also aberrantly expressed as a fusion transcript with AML1 (AML1/**Evi-1**), which leads to blastic transformation in patients with chronic myelogenous leukemia. We previously showed that **Evi-1** and AML1/**Evi-1** block the antiproliferative effect of TGF-beta. They represses TGF-beta signaling by direct interaction with Smad3 through their first zinc finger motif. Here, we demonstrate that **Evi-1** represses Smad-induced transcription by recruiting **CtBP** as a **corepressor**. **CtBP** was originally identified as a protein which interacts with C-terminal region of adenoviral oncoprotein E1A. **CtBP** is ubiquitously expressed including hematopoietic cells, and has been shown to act as a **corepressor** of certain transcriptional repressors, such as BKLF, FOG, and TCF. We show that **Evi-1** directly associates with **CtBP1** through one of the consensus binding motifs, and this association is required for efficient inhibition of TGF-beta signaling. A specific inhibitor for histone deacetylase (HDAC) alleviates **Evi-1**-mediated repression of TGF-beta signaling, suggesting that HDAC is involved in the transcriptional repression by **Evi-1**. This identifies a novel function of **Evi-1** as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms for **Evi-1**-induced leukemogenesis.

L28 ANSWER 29 OF 33 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
 STN
 ACCESSION NUMBER: 2000:103749 BIOSIS
 DOCUMENT NUMBER: PREV200000103749
 TITLE: Multiple modes of repression by the **Smad**
 transcriptional corepressor TGIF.
 AUTHOR(S): Wotton, David; Lo, Roger S.; Swaby, Laurie-Anne C.;
 Massague, Joan [Reprint author]
 CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New
 York, NY, 10021, USA
 SOURCE: Journal of Biological Chemistry, (Dec. 24, 1999) Vol. 274,
 No. 52, pp. 37105-37110. print.
 CODEN: JBCHA3. ISSN: 0021-9258.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 22 Mar 2000
 Last Updated on STN: 3 Jan 2002

AB TGIF is a DNA-binding homeodomain protein that has been demonstrated to play a role in transforming growth factor beta-regulated transcription and implicated in the control of retinoid-responsive transcription. We investigated the intrinsic transcriptional activity of TGIF fused to a

heterologous DNA-binding domain. Our results demonstrate that TGIF is a transcriptional repressor able to repress transcription from several different promoters. Repression by TGIF is insensitive to the distance at which it is bound from the promoter. Moreover, the wild type TGIF effectively represses transcription when bound to its cognate DNA-binding site via its homeodomain. Deletion analysis revealed the presence of at least two separable repression domains within TGIF. Repression by one of these is dependent on the activity of histone deacetylases (HDACs), whereas the other appears not to require HDAC activity. Finally, we demonstrate that TGIF interacts with HDACs via its carboxyl-terminal repression domain. Together, these results suggest that TGIF is a multifunctional transcriptional repressor, which acts in part by recruiting HDAC activity.

L28 ANSWER 30 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation.
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ACCESSION NUMBER: 2003:445536 SCISEARCH
THE GENUINE ARTICLE: 680BU
TITLE: Opposing functions of ZEB proteins in the regulation of the TGF beta/BMP signaling pathway
AUTHOR: Postigo A A (Reprint)
CORPORATE SOURCE: Washington Univ, Sch Med, Dept Internal Med, Div Mol Oncol, St Louis, MO 63110 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: EMBO JOURNAL, (15 MAY 2003) Vol. 22, No. 10, pp. 2443-2452

Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.

ISSN: 0261-4189.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 66

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Binding of TGFbeta/BMP factors to their receptors leads to translocation of **Smad** proteins to the nucleus where they activate transcription of target genes. The two-handed zinc finger proteins encoded by Zfhx1a and Zfhx1b, ZEB-1/deltaEF1 and ZEB-2/**SIP1**, respectively, regulate gene expression and differentiation programs in a number of tissues. Here I demonstrate that ZEB proteins are also crucial regulators of TGFbeta/BMP signaling with opposing effects on this pathway. Both ZEB proteins bind to Smads, but while ZEB-1/deltaEF1 synergizes with **Smad** proteins to activate transcription, promote osteoblastic differentiation and induce cell growth arrest, the highly related ZEB-2/**SIP1** protein has the opposite effect. Finally, the ability of TGFbeta to mediate transcription of TGFbeta-dependent genes and induce growth arrest depends on the presence of endogenous ZEB-1/deltaEF1 protein.

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ACCESSION NUMBER: 2003:151974 SCISEARCH

THE GENUINE ARTICLE: 643XN

TITLE: Nuclear convergence of the **TGF beta** and cAMP signal transduction pathways in murine embryonic palate mesenchymal cells

AUTHOR: Warner D R (Reprint); Pisano M M; Greene R M

CORPORATE SOURCE: Univ Louisville, Sch Dent, Birth Defects Ctr, Dept Mol Cellular & Craniofacial Biol, 501 S Preston St, Suite 301, Louisville, KY 40292 USA (Reprint); Univ Louisville, Sch Dent, Birth Defects Ctr, Dept Mol Cellular & Craniofacial Biol, Louisville, KY 40292 USA

COUNTRY OF AUTHOR: USA

SOURCE: CELLULAR SIGNALLING, (FEB 2003) Vol. 15, No. 2, pp. 235-242.

Publisher: ELSEVIER SCIENCE INC, 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.

DOCUMENT TYPE: Article; Journal
 LANGUAGE: English
 REFERENCE COUNT: 40
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
 AB **Transforming growth factors beta**
 (TGF β) and cyclic AMP (cAMP) both participate in growth and differentiation of the developing mammalian secondary palate and elicit similar biological responses. Cross-talk between these two signal transduction pathways in cells derived from the embryonic palate has been demonstrated previously. In the present study, we have examined nuclear convergence of these signalling pathways at the level of transcriptional complex formation. Biotinylated oligonucleotides encoding a consensus Smad binding element (SBE), or a cyclic AMP response element (CRE), were mixed with cell extracts from murine embryonic palate mesenchymal (MEPM) cells that were treated with either TGF β or forskolin. Protein-oligonucleotide complexes were precipitated with streptavidin-agarose, and analysed by Western blotting to identify proteins in the complex bound to each consensus oligonucleotide. TGF β treatment of MEPM cells increased the levels of phosphorylated Smad2, phosphorylated cAMP response element binding protein (CREB), and the coactivator, CREB binding protein (CBP), that were part of a complex bound to the SBE. Treatment of cells with forskolin, a stimulator of adenylate cyclase, increased the amount of phosphorylated CREB and CBP, but not the amount of phosphorylated Smad2 bound in a complex to the SBE. Additionally, the presence of the co-repressors, c-Ski and SnoN, was demonstrated as part of a complex bound to the SBE (but not the CRE). Amounts of c-Ski and SnoN found in the SBE-containing complex increased in response to either TGF β or forskolin. These results demonstrate that phosphorylated CREB forms a complex with the co-activator CBP, phosphorylated Smad2 and the co-repressors c-Ski and SnoN on a consensus SBE. This suggests cooperative regulation of genes with SBE-containing promoters by the cAMP and TGF β signalling pathways in the developing palate. (C) 2003 Elsevier Science Inc. All rights reserved.

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 on STN
 ACCESSION NUMBER: 2002:600632 SCISEARCH
 THE GENUINE ARTICLE: 571XC
 TITLE: Overlapping and unique roles for C-terminal binding protein 1 (CtBP1) and CtBP2 during mouse development.
 AUTHOR: Hildebrand J D (Reprint); Soriano P
 CORPORATE SOURCE: Univ Pittsburgh, Dept Biol Sci, 5th & Ruskin Ave, Pittsburgh, PA 15260 USA (Reprint); Univ Pittsburgh, Dept Biol Sci, Pittsburgh, PA 15260 USA; Fred Hutchinson Canc Res Ctr, Program Dev Biol, Seattle, WA 98108 USA; Fred Hutchinson Canc Res Ctr, Div Basic Sci, Seattle, WA 98108 USA
 COUNTRY OF AUTHOR: USA
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (AUG 2002) Vol. 22, No. 15, pp. 5296-5307.
 Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.
 ISSN: 0270-7306.
 DOCUMENT TYPE: Article; Journal
 LANGUAGE: English
 REFERENCE COUNT: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The C-terminal binding protein (CtBP) family of proteins has been linked to multiple biological processes through their association with numerous transcription factors. We generated mice harboring mutations in both Ctbp1 and Ctbp2 to address the in vivo function of CtBPs during vertebrate development. Ctbp1 mutant mice are small but viable and fertile, whereas Ctbp2-null mice show defects in axial

patterning and die by E10.5 due to aberrant extraembryonic development. Mice harboring various combinations of *Ctbp1* and *Ctbp2* mutant alleles exhibit dosage-sensitive defects in a wide range of developmental processes. The strong genetic interaction, as well as transcription assays with CtBP-deficient cells, indicates that CtBPs have overlapping roles in regulating gene expression. We suggest that the observed phenotypes reflect the large number of transcription factors whose activities are compromised in the absence of CtBP.

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ACCESSION NUMBER: 2000:475743 SCISEARCH
THE GENUINE ARTICLE: 325ZM
TITLE: TGF-**beta** signaling by Smad proteins
AUTHOR: Miyazono K (Reprint)
CORPORATE SOURCE: JAPANESE FDN CANC RES, INST CANC, DEPT BIOCHEM, TOSHIMA KU, 1-37-1 KAMI IKEBUKURO, TOKYO 1708455, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: CYTOKINE & GROWTH FACTOR REVIEWS, (MAR-JUN 2000) Vol. 11, No. 1-2, pp. 15-22.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 1359-6101.

DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Smads are signal transducers for the members of the transforming growth factor-p (TGF-P) superfamily. **Bone morphogenetic** proteins (**BMPs**) and their receptors induce differentiation of C2C12 cells into osteoblast-like cells. Using an adenoviral expression vector system, we showed that receptor-regulated Smads (R-Smads) activated by **BMPs** can induce the differentiation of C2C12 cells. Inhibitory Smads (I-Smads) interfere with the osteoblast differentiation of C2C12 cells by preventing the nuclear translocation of R-Smads. After translocation into the nucleus, Smad oligomers regulate the transcription of target genes through **binding** to DNA directly, **interaction** with other DNA **binding** proteins, and recruitment of **transcriptional** co-activators or co-**repressors**. Through **interaction** with different **transcription** factors and **transcriptional** co-activators or **co-repressors**, Smads may exhibit specific effects in various cell types. (C) 2000 Elsevier Science Ltd. All rights reserved.